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Polycyclic N-Hetero Compounds. XIV.[1] Reactions of Methylpyridines with Formamide

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Reactions of pyridines and condensed pyridines having active methyl group with formamide were described. 2- or 4-methylpyridine (I, IV) gave 5-(2- or 4-pyridyl)-pyrimidine (II, V). 2- or 4-methylquinoline (VI, XI) gave 2- or 4-(5-pyrimidinyl)-quinoline (VII, XII) and 1-formyl-2- or 4-methyl-1,2,3,4-tetrahydroquinoline (IX, XIII). 3,5-Di(2-quinolyl)pyridine (VIII) and 2-(2-pyrazinyl)quinoline (X) were obtained from VI except for VII and IX. 3-Methylisoquinoline (XIV) gave 2-formyl-3-methyl-1,2,3,4-tetrahydroisoquinoline (XV) and quinoline (XVI) gave 1,2,3,4-tetrahydroquinoline (XVIII) and its N-formyl derivative (XVII). Purine (III) was confirmed on thin-layer chromatography in these reactions.

Keywords——formamide; methylpyridines and condensed pyridines; pyrimidinyl cyclization of active methyl group; pyrimidinylpyridines and condensed pyridines; reduction of condensed pyridines; N-formyl-1,2,3,4-tetrahydro condensed pyridines; purine

The previous paper[3] reported that the reactions of 4-methylpyrimidines with formamide in the presence of phosphoryl chloride, or with trisformylaminomethane in formamide afforded 4-(5-pyrimidinyl)pyrimidines. To extend this facile one-step pyrimidinyl cyclization, the present paper deals with the reactions of pyridines or condensed pyridines having active methyl group which will be considered less reactive than 4-methylpyrimidines.

As shown in Chart 1, 2-methylpyridine (I), 4-methylpyridine (IV), 2-methylquinoline (VI), 4-methylquinoline (XI), and 3-methylisoquinoline (XIV) were used as starting materials.

Heating of I with formamide at 160—180° for 17 hr gave 5-(2-pyridyl)pyrimidine (II). The proton magnetic resonance (PMR) spectrum exhibited disappearance of methyl group and appearance of one-proton singlet at δ 9.31 and two-proton singlet at δ 9.38 attributable to pyrimidine ring protons. Reaction of IV with formamide gave 5-(4-pyridyl)pyrimidine (V) which had already been synthesized by Arnold[4] on heating 4-pyridylmalonaldehyde with methanolic ammonia in autoclave. Similar reaction of VI afforded 2-(5-pyrimidinyl)quinoline (VII) expected, 3,5-di(2-quinolyl)pyridine (VIII), 1-formyl-2-methyl-1,2,3,4-tetrahydroquinoline (IX),[5] and an isomer (X) of VII (the structure of which will be perhaps 2-(2-pyrazinyl)-quinoline). The PMR spectrum of VIII exhibited one-proton triplet (J=2 Hz) at δ 9.33 and two-proton doublet (J=2 Hz) at δ 9.49 attributable to pyridine ring protons. Similar ob-

1) Part XIII: T. Koyama, T. Nanba, T. Hirota, S. Ohmori, and M. Yamato, *Chem. Pharm. Bull.* (Tokyo), **25**, 964 (1977).
2) Location: *1-1 Tsushima-naka 1-chome, Okayama, 700, Japan.*
3) T. Koyama, T. Hirota, Y. Shinohara, S. Matsumoto, S. Ohmori, and M. Yamato, *Chem. Pharm. Bull.* (Tokyo), **23**, 2029 (1975); T. Koyama, T. Hirota, C. Bashou, Y. Satou, Y. Watanabe, S. Ohmori, and M. Yamato, *Chem. Pharm. Bull.* (Tokyo), **23**, 2158 (1975); T. Koyama, T, Hirota, C. Bashou, Y. Watanabe, Y. Kitauchi, Y. Satou, S. Ohmori, and M. Yamato, *Chem. Pharm. Bull.* (Tokyo), **24**, 1459 (1976).
4) Z. Arnold, *Collect. Czech. Chem. Commun.*, **28**, 863 (1963).
5) B.A. Lugovik, L.G. Yudin, A.M. Popov, and A.A. Kovaneva, *Vestn. Mosk. Univ. Khim.*, **12**, 601 (1971) [*C.A.*, **76**, 46057*w* (1972)].

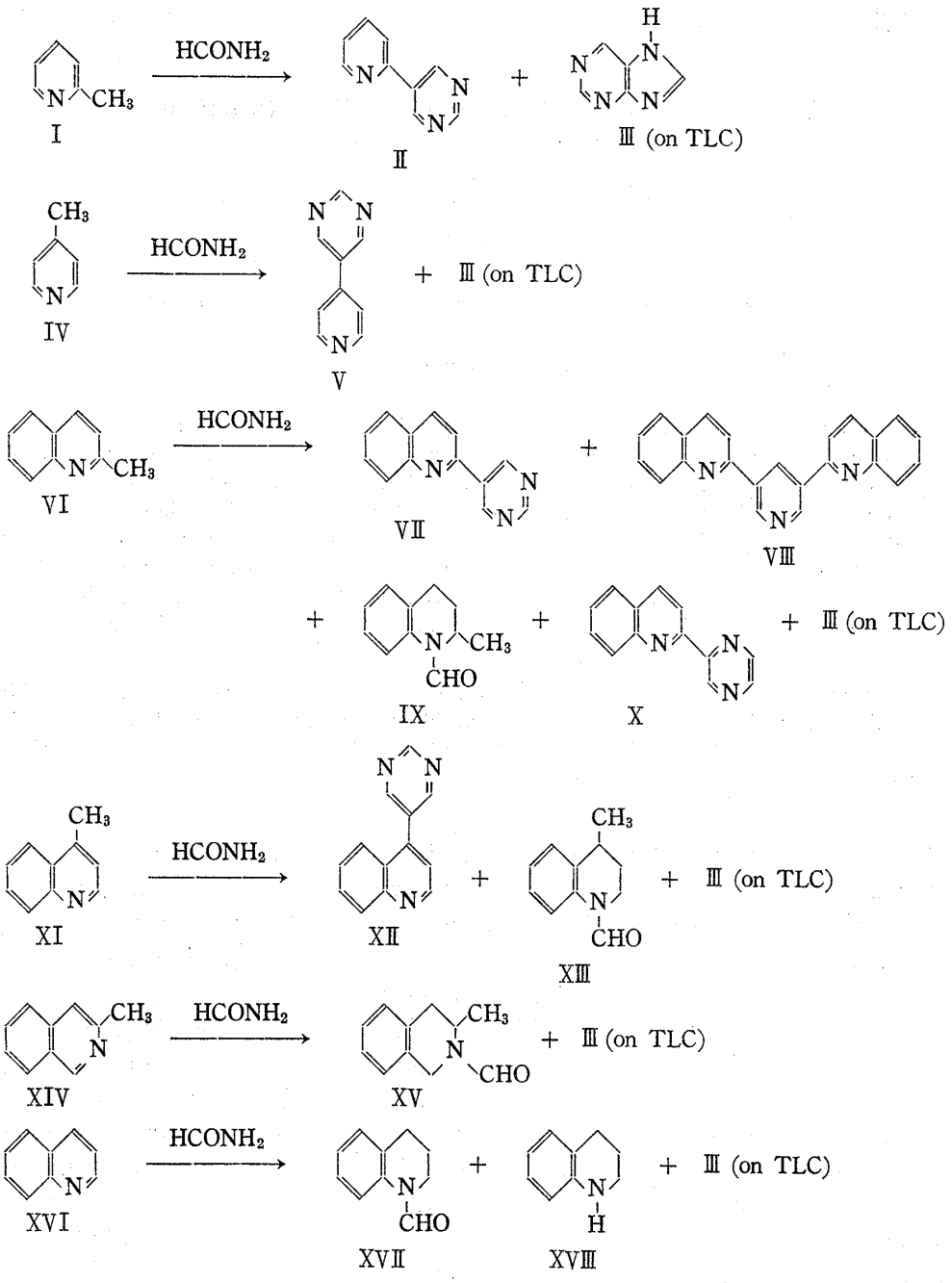


Chart 1

servation of pyridine ring formation was reported by Eckroth[6] as an abnormal Tschitschibabin reaction, *i.e.*, reduction of *m*-methoxyphenylacetamide with lithium aluminum hydride in boiling tetrahydrofuran gave 3,5-bis(*m*-methoxyphenyl)pyridine. In which reaction, formation of *m*-methoxyphenylacetamidine-enamine tautomer was presumed and condensation of three molecules of these tautomers gave 3,5-bis(*m*-methoxyphenyl)pyridine with loss of *m*-methylanisole. Analogous mechanism is indicated in Chart 2.

IX had already been synthesized by Lugovik, *et al.*[5] from VI and formic acid in vapor phase (230—250°), therefore formation of IX in our experiment suggested that quinoline ring was reduced by formic acid formed from thermal decomposition of formamide and formylation occurred simultaneously. The related some works reported that reduction of quinoline

6) D.R. Eckroth, *Chem. Ind.* (London), **1967**, 920.

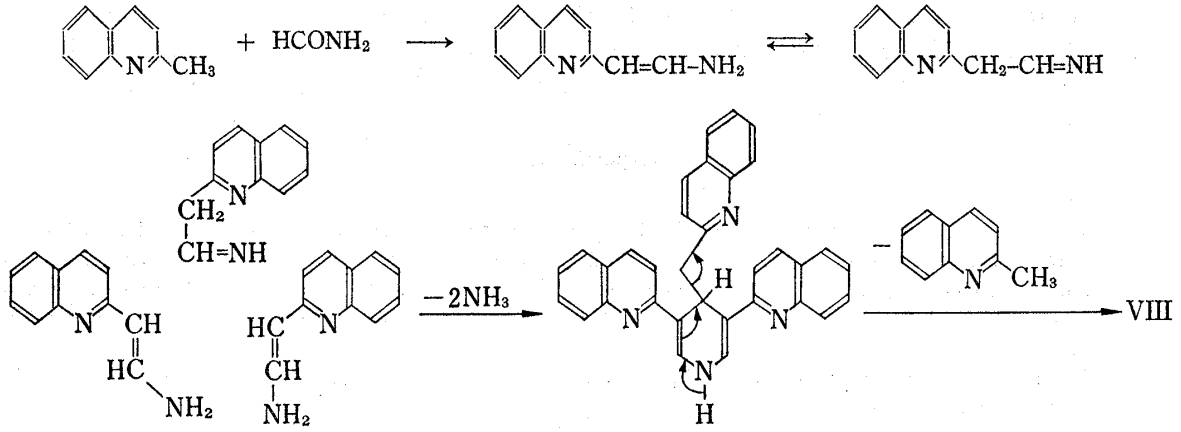
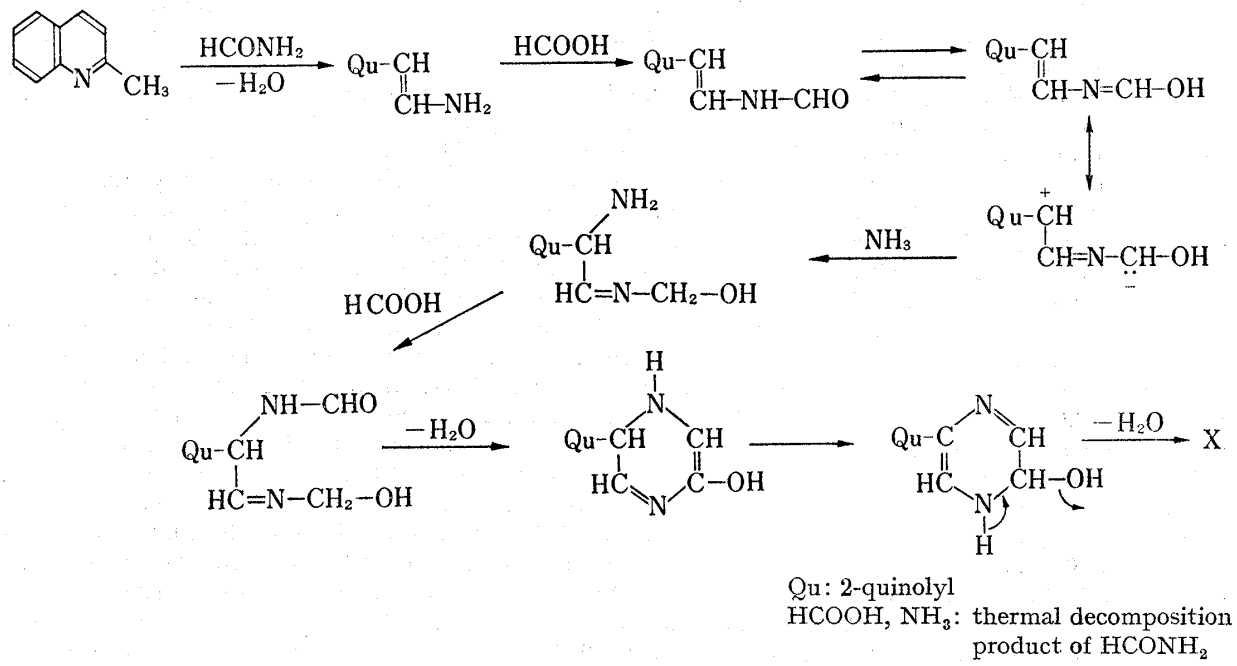


Chart 2

or isoquinoline with formic acid-triethylamine,[7] formamide–formic acid,[8] and formic acid–sodium formate[8] gave N-formyl-1,2,3,4-tetrahydroquinoline or isoquinoline, but there is no report with formamide only. Elemental analysis and mass spectral (MS) data of X agreed with $C_{13}H_9N_3$ and its PMR spectrum exhibited one-proton doublet (J=2.6 Hz) at δ 9.57 attributable to pyrazine-5-H, one-proton doublet (J=1.5 Hz) at δ 9.23 for pyrazine-3-H, and one-proton double doublet (J=2.6 Hz, 1.5 Hz) at δ 8.89 for pyrazine-6-H. The presumable formation mechanism of X is shown in Chart 3.



Qu: 2-quinolyl
HCOOH, NH_3: thermal decomposition product of $HCONH_2$

Chart 3

Condensation of XI with formamide gave 4-(5-pyrimidinyl)quinoline (XII) and 1-formyl-4-methyl-1,2,3,4-tetrahydroquinoline (XIII). Similar reaction of XIV gave 2-formyl-3-methyl-1,2,3,4-tetrahydroisoquinoline (XV) without isolation of 3-(5-pyrimidinyl)isoquinoline. Heating of quinoline (XVI) itself with formamide gave 1-formyl-1,2,3,4-tetrahydroquinoline (XVII)[8] and 1,2,3,4-tetrahydroquinoline (XVIII).[9]

7) S. Durand, X. Lusinchi, and R.C. Morean, *Bull. Soc. Chim. Fr.*, **1961**, 270.
8) A.N. Kost and L.G. Yudin, *Zhur. Obshchei Khim.*, **25**, 1947 (1955) [*C.A.*, **50**, 8644 (1956)].
9) J. Braun, A. Petzold, and J. Seemann, *Chem. Ber.*, **55**, 3783 (1920).

Okamoto and Yamada[10] described formation of purine by heating formamide at 170—190° for 28 hr. Since our reaction condition was similar to that of them, purine (III) was observed in above all reactions on thin-layer chromatography (TLC) as expected.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were recorded on Nippon Bunko DS-301 spectrometer. PMR spectra were taken on a Hitachi R-22 spectrometer (90 MHz) with tetramethylsilane as an internal standard (δ value), s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. MS were obtained with Shimadzu LKB-9000 instrument. Ultraviolet (UV) spectra were taken on a Hitachi ESP-2 spectrophotometer in 99% EtOH.

Reaction of 2-Methylpyridine (I) with Formamide——A mixture of 4.9 ml (0.05 mol) of I and 20 ml (0.5 mol) of $HCONH_2$ was heated at 160—180° for 27 hr under stirring. After cooled, the reaction mixture was suspended with sat. NaCl solution and extracted with benzene. The benzene layer was washed with sat. NaCl solution, dried over Na_2SO_4, and evaporated. The residue was recrystallized from cyclohexane to give 0.44 g (5.6%) of 5-(2-pyridyl)pyrimidine (II) as colorless needles, mp 128—131°. For elemental analysis, the crystals were subjected to high vacuum sublimation followed by recrystallization from cyclohexane, colorless needles, mp 130—131°. *Anal.* Calcd. for $C_9H_7N_3$: C, 68.77; H, 4.49; N, 26.74. Found: C, 68.44; H, 4.61; N, 26.49. MS *m/e* (M^+): 157. UV λ_{max}^{EtOH} nm (log ε): 239 (4.40), 267 (4.37). PMR ($CDCl_3$): 7.30 (1H, m), 7.82 (2H, m), 8.78 (1H, dd, J=5 Hz, 2 Hz)-pyridine ring-H, 9.31 (1H, s, pyrimidine-2-H), 9.38 (2H, s, pyrimidine-4,6-H).

Reaction of 4-Methylpyridine (IV) with $HCONH_2$——A mixture of 4.9 ml (0.05 mol) of IV and 20 ml (0.5 mol) of $HCONH_2$ was heated at 160—180° for 17 hr under stirring. The reaction mixture was treated as described above. The residue was recrystallized from cyclohexane to give 0.32 g (4%) of 5-(4-pyridyl)-pyrimidine (V)[4] as colorless needles, mp 105—108°. For elemental analysis, the crystals were subjected to high vacuum sublimation, mp 107—108° (reported mp 107.5—108.5°[4]). *Anal.* Calcd. for $C_9H_7N_3$: C, 68.77; H, 4.49; N, 26.74. Found: C, 68.59; H, 4.61; N, 26.50. MS *m/e* (M^+): 157. UV λ_{max}^{EtOH} nm (log ε): 238 (4.49). PMR ($CDCl_3$): 7.55, 8.80 (each 2H, dd, J=4.5 Hz, 2 Hz, pyridine-H), 9.00 (2H, s, pyrimidine-4,6-H), 9.31 (1H, s, pyrimidine-2-H).

Reaction of 2-Methylquinoline (VI) with Formamide——A mixture of 4.0 ml (0.03 mol) of VI and 12 ml (0.3 mol) of $HCONH_2$ was heated at 170—180° for 29 hr under stirring. The reaction mixture was treated as described above. The residue was subjected to fractional distillation under reduced pressure. (a) The yellowish oily distillate of bp 60—70°/below 0.003 mmHg was determined 1-formyl-2-methyl-1,2,3,4-tetrahydroquinoline (IX), yield 0.62 g (11.5%). *Anal.* Calcd. for $C_{11}H_{13}ON$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.10; H, 7.55; N, 7.86. MS *m/e* (M^+): 175. IR ν_{max}^{liquid} cm^{-1}: 1666 (C=O). PMR ($CDCl_3$): 1.19 (3H, d, J=7 Hz, CH_3), 1.87, 2.71 (each 2H, m, 3,4-H), 4.78 (1H, m, 2-H), 7.11 (4H, m, 5,6,7,8-H), 8.61 (1H, s, CHO). (b) The fraction of bp 80—100°/below 0.003 mmHg, which was solidified, was fractionated with preparative TLC (Merck Kiesel guhr PF_{254}; acetone: benzene: cyclohexane=2: 1: 1). (b′) The fraction of *Rf* value *ca.* 0.6—0.7 was recrystallized from cyclohexane to give 0.34 g (5.6%) of 2-(5-pyrimidinyl)quinoline (VII) as colorless feathers, mp 139—140°. *Anal.* Calcd. for $C_{13}H_9N_3$: C, 75.34; H, 4.38; N, 20.28. Found: C, 75.34; H, 4.37; N, 20.31. MS *m/e* (M^+): 207. UV λ_{max}^{EtOH} nm (log ε): 209 (4.20), 251 (4.45). PMR ($CDCl_3$): 7.68 (3H, m, quinoline-5,6,7-H), 7.87, 8.32 (each 1H, AB q, J=9 Hz, quinoline-3,4-H), 8.21 (1H, bd, J=8 Hz, quinoline-8-H), 9.33 (1H, s, pyrimidine-2-H), 9.66 (2H, s, pyrimidine-4,6-H). (b″) The fraction of *Rf* value *ca.* 0.3—0.4 was recrystallized from cyclohexane to give 0.32 g (5.4%) of 2-(2-pyrazinyl)quinoline (X) as colorless fine needles, mp 156—157°. *Anal.* Calcd. for $C_{13}H_9N_3$: C, 75.34; H, 4.38; N, 20.28. Found: C, 75.40; H, 4.36; N, 20.13. MS *m/e* (M^+): 207. UV λ_{max}^{EtOH} nm (log ε): 249 (4.26), 263 (4.18), 299 (3.96). PMR ($CDCl_3$): 7.51—8.22 (5H, m, quinoline-4,5,6,7,8-H), 8.81 (1H, d, J=6.5 Hz, quinoline-3-H), 8.89 (1H, dd, J=2.6 Hz, 1.5 Hz, pyrazine-6-H), 9.23 (1H, d, J=1.5 Hz, pyrazine-3-H), 9.57 (1H, d, J=2.6 Hz, pyrazine-5-H). (c) The fraction of sublimating point 200—220°/below 0.003 mmHg was recrystallized from EtOH to give 0.22 g (4.4%) of 3,5-di(quinolyl)pyridine (VIII) as colorless scales, mp 233—234°. *Anal.* Calcd. for $C_{23}H_{15}N_3$: C, 82.86; H, 4.54; N, 12.61. Found: C, 82.63; H, 4.55; N, 12.55. MS *m/e* (M^+): 333. UV λ_{max}^{EtOH} nm (log ε): 211 (4.36), 254 (4.60), 298 (4.04). PMR ($CDCl_3$): 7.46—8.01 (6H, m, 2-quinoline-5,6,7-H), 8.01, 8.29 (each 2H, AB q, J=8 Hz, 2-quinoline-3,4-H), 8.21 (2H, bd, J=7 Hz, 2-quinoline-8-H), 9.33 (1H, t, J=2 Hz, pyridine-4-H), 9.49 (2H, d, J=2 Hz, pyridine-2,6-H).

Reaction of 4-Methylquinoline (XI) with $HCONH_2$——A mixture of 4.3 g (0.03 mol) of XI and 12 ml (0.3 mol) of $HCONH_2$ was heated at 180—190° for 16 hr under stirring. The reaction mixture was treated as described above ($(C_2H_5)_2O$ was used as extracting solvent). The residual viscous oil was chromatographed over silica gel with benzene. The benzene eluate was fractionated with preparative TLC (Merck Kiesel guhr PF_{254}; benzene: $(C_2H_5)_2O$=2: 1). The fraction of *Rf* value *ca.* 0.7 was collected and subjected to vacuum

10) T. Okamoto and H. Yamada, *Chem. Pharm. Bull.* (Tokyo), **20**, 623 (1972).

distillation to give 0.57 g (11%) of 1-formyl-1,2,3,4-tetrahydroquinoline (XIII) as slightly yellowish green oil, bp 146—150°/3—4 mmHg. *Anal.* Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.09; H, 7.48; N, 7.73. MS *m/e* (M^+): 175. IR ν_{max}^{liquid} cm^{-1}: 1665 (C=O). PMR ($CDCl_3$): 1.30 (3H, d, $J=7$ Hz, CH_3), 1.85 (2H, m, 3-H), 2.93 (1H, m, 4-H), 3.81 (2H, m, 2-H), 7.20 (4H, m, 5,6,7,8-H), 8.79 (1H, s, CHO).

The $(C_2H_5)_2O$ eluate of column chromatography was recrystallized from benzene–cyclohexane (*ca.* 1: 1) to give 0.24 g (4%) of 4-(5-pyrimidinyl)quinoline (XII) as pale yellow needles, mp 149—152°. For elemental analysis, the crystals were subjected to high vacuum sublimation, colorless needles, mp 152—153°. *Anal.* Calcd. for $C_{13}H_9N_3$: C, 75.34; H, 4.38; N, 20.28. Found: C, 75.09; H, 4.50; N, 20.11. MS *m/e* (M^+): 207. UV λ_{max}^{EtOH} nm (log ε): 230.5 (4.58), 293 (4.34), 303.5 (4.34), 317 (4.16). PMR ($CDCl_3$): 7.33, 8.97 (each 1H, AB q, $J=5$ Hz, quinoline-3,2-H), 7.40—8.30 (4H, m, quinoline-5,6,7,8-H), 8.87 (2H, s, pyrimidine-4,6-H), 9.33 (1H, s, pyrimidine-2-H).

Reaction of 3-Methylisoquinoline (XIV) with $HCONH_2$——A mixture of 2.86 g (0.02 mol) of XIV and 8 ml (0.2 mol) of $HCONH_2$ was heated at 180—190° for 20 hr under stirring. The reaction mixture was treated as described above. The residue was chromatographed over silica gel with benzene. The first benzene eluate (*ca.* 400 ml) contained 0.75 g (38%) of XIV and the second benzene eluate was distilled under reduced pressure to give 0.33 g (13.5%) of 2-formyl-3-methyl-1,2,3,4-tetrahydroisoquinoline (XV) as pale yellow oil, bp 145—150°/3—4 mmHg. *Anal.* Calcd. for $C_{11}H_{13}NO$: C, 75.40; H, 7.48; N, 7.99. Found: C, 75.11; H, 7.40; N, 8.08. IR ν_{max}^{liquid} cm^{-1}: 1660 (C=O, broad). PMR ($CDCl_3$): 1.19, 1.24 (3H, each d, $J=7$ Hz, CH_3), 2.41—3.25 (2H, doublets of AB quartets were overlapped, 4-H), 3.8—5.1 (3H, m, 1,3-H), 7.16 (4H, m, 5,6,7,8-H), 8.19, 8.22 (1H, each s, CHO). The PMR data suggested the inversion of tetrahydropyridine ring as described by Dalton, *et al.*[11] in 2-acetyl-1,2,3,4-tetrahydroisoquinoline.

Reaction of Quinoline (XVI) with $HCONH_2$——A mixture of 6.45 g (0.05 mol) of XVI and 20 ml (0.5 mol) of $HCONH_2$ was heated at 180—190° for 15 hr under stirring. The reaction mixture was treated as described above ($(C_2H_5)_2O$ was used as extracting solvent). The residue was chromatographed over alumina with cyclohexane. The cyclohexane eluate was distilled under reduced pressure to give 0.54 g (8%) of 1,2,3,4-tetrahydroquinoline (XVIII) as pale brown oil, bp 125—127°/16—17 mmHg.[9] *Anal.* Calcd. for $C_9H_{11}N$: C, 81.16; H, 8.33; N, 10.52. Found: C, 81.30; H, 8.15; N, 10.41. The IR and PMR spectra agreed with the authentic sample.[12] The benzene eluate was distilled under reduced pressure to give 1.61 g (20%) of 1-formyl-1,2,3,4-tetrahydroquinoline (XVII) as pale yellow oil. bp 141—145°/3—4 mmHg.[8] *Anal.* Calcd. for $C_{10}H_{11}NO$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.30; H, 7.02; N, 8.48. The IR and PMR spectra agreed with authentic sample.[8]

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11) D.R. Dalton, K.C. Ramey, H.J. Gisler, Jr., L.J. Lendvay, and A. Abraham, *J. Am. Chem. Soc.*, **91**, 6367 (1965).
12) The Aldrich Library of IR Spectra and NMR Catalogue.